unsigned

IAF-14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#23
11-3-95

Examiner	:	C.Tsang
Group Art Unit	:	1202
Applicants	:	Coates et al.
Serial No:	:	07/835,964
Filed	:	February 20, 1992
For	:	1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES

DECLARATION OF HUGH MCDADE
UNDER 37 C.F.R. § 1.132

I, Hugh McDade, declare and state as follows:

1. I obtained a medical degree (M.B. Ch.B) with commendation from Glasgow University, Scotland in 1971. I have been licensed to practice medicine in the United Kingdom since 1972 and became a Fellow of the Royal College of Physicians and Surgeons of Glasgow in 1991.

2. After completing my training in general medicine, I entered the pharmaceutical industry in 1981. For the past ten years, I have been responsible for the design, conduct and analysis of various local and international clinical trials with antibiotics, antivirals and anticancer agents. I am a co-author on several papers in the anti-infective area. I am an appointed referee for

the Journal of Antimicrobial Chemotherapy and sit on the Council of the British Society of Antimicrobial Chemotherapy.

I am currently the European Director of Antiviral Clinical Research for Glaxo Wellcome plc. At Glaxo Wellcome, I supervise a staff of 16 clinical research scientists in their conduct of international clinical trials in HIV disease, chronic hepatitis B and influenza.

3. I have been involved with the clinical trials of 3TC™ (a formulation of the nucleoside analog (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one) for the treatment of human immunodeficiency virus (HIV) disease since the first administration of that nucleoside analog to man through to Glaxo's applications for FDA approval in the United States and corresponding approval in Europe and Canada. In fact, I have been and continue to be responsible for the design and analysis of the majority of the clinical trials on 3TC™ to date and have prepared data from these trials for presentation at international meetings.

4. I have read United States patent application 07/835,964, filed February 20, 1992, which claims priority from Great Britain patent application 9009861.7, filed May 2, 1990. I am aware that the Examiner charged with

examination of United States patent application 07/835,964 believes that it does not teach the ordinary skilled person how to use 3TC™.

5. I make this declaration to set forth the qualifications of a person of ordinary skill in the art of using nucleoside analogs to treat viral infections in May 1990 and to explain why I believe that United States patent application 07/835,964 would have taught such persons how to use 3TC™. I understand that this declaration is being submitted the United States Patent and Trademark Office in connection with the prosecution of application 07/835,964.

6. I believe that on May 2, 1990, the priority date of United States patent application 07/835,964, a person of ordinary skill in the art of using nucleoside analogs to treat viral infections would be team of persons with several years of experience in the field of pharmacology, toxicology and clinical medicine ("the skilled worker"). I also believe that on May 2, 1990, such person, with United States patent application 07/835,964 in hand, would have known how to use 3TC to treat viral infections. In my view, on that date, the skilled worker would have been able to use 3TC™ to treat viral infection using only routine experimentation, without the exercise of inventive skill.

7. United States patent application 07/835,964 teaches that (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or 3TC™ is very active against HIV *in vitro* with relatively low toxicity.

Based on this information, the skilled worker would immediately know how to take (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one through the necessary safety testing and clinical trials to allow its registration for marketing and sale. This is particularly true in the case of 3TC™ because specific guidelines and protocols for the testing of AZT (which had been approved by the United States Food and Drug Administration in 1987) and other nucleoside analogues (such as ddI which was under clinical investigation in 1990) had already been established and widely published.

8. Based on the information provided in United States patent application 07/835,964, the skilled worker, in my view, would first have conducted animal studies designed to determine the *in vivo* toxicity and bioavailability of (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. These studies are routinely performed before any promising pharmaceutical is tested in humans. Protocols for such testing are standard in the industry.

With the data derived from the toxicity and bioavailability studies, (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-1H)-pyrimidin-2-one would be manufactured in pill form in a low dosage. Such procedures are also standard in the industry.

Finally, the skilled worker would conduct dose escalation studies and clinical trials. Such studies and trials would be easily designed using well known and often used protocols. From these trials, the skilled worker would know the most preferred way to dose and use 3TC™ to treat viral infections.

9. I understand that numerous publications detailing the actual clinical trials of 3TC™ have been submitted to the Examiner in connection with this application. In my view, neither the design nor the implementation of these clinical trials required undue experimentation. Nor do I believe that the animal studies or preparation of the pharmaceutical formulation of 3TC™ prior to these clinical trials required undue experimentation.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the

knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

_____
Hugh McDade

Signed at: _____

Date: _____, 1995

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON D.C. 20231, on

September 27, 1995

Thomas Quinones
Name of Person Signing

Signature of Person Signing